PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 9/24 — A1

(11) International Publication Number: WO 94/09761

(43) International Publication Date: 11 May 1994 (11.05.94)

(21) International Application Number: PCT/US93/09873

(22) International Filing Date: 21 October 1993 (21.10.93)

(30) Priority data:
07/965,470 23 October 1992 (23.10.92) US

(60) Parent Application or Grant
(63) Related by Continuation
US 07/965,470 (CIP)
Filed on 23 October 1992 (23.10.92)

(71) Applicant *(for all designated States except US)*: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : KWAN, Henry, K. [GB/US]; 37 Knob Hill Drive, Summit, NJ 07901 (US). LIEBOWITZ, Stephen, M. [US/US]; 70 Beechwood Circle, Neshanic Station, NJ 08853 (US).

(74) Agents: HOFFMAN, Thomas, D. et al.; Schering-Plough Corporation, One Giralda Farms, M3W, Madison, NJ 07940-1000 (US).

(81) Designated States: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: STABLE EXTENDED RELEASE ORAL DOSAGE COMPOSITION

(57) Abstract

A film-coated extended release oral dosage composition containing the nasal decongestant pseudoephedrine or salt thereof, e.g., pseudoephedrine sulfate in a unique polymer matrix core and a film-coating on such core containing the non-sedating antihistamine, loratadine, and use of the said composition for treating patients showing the signs and symptoms associated with upper respiratory diseases and nasal congestion are disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

STABLE EXTENDED RELEASE ORAL DOSAGE COMPOSITION

BACKGROUND OF THE INVENTION

This invention relates to a film-coated extended release oral dosage composition containing the nasal decongestant pseudephedrine in a unique polymer matrix core and a film-coating on such core containing the non-sedating antihistamine, loratadine. The oral dosage composition of this invention is useful for treating patients showing the signs and symptoms associated with the common cold, upper respiratory diseases, allergic rhinitis and nasal congestion.

Loratadine is disclosed in USP 4,282, 233 as a non-sedating antihistamine and it is useful as an anti-allergy agent in, for example, the treatment of seasonal allergic rhinitis symptoms such as sneezing and itching.

Pseudephedrine as well as pharmaceutically acceptable acid additional salts, e.g., those of HCl or H_2SO_4, is a sympathomimetic drug recognized by those skilled in the art as a safe therapeutic agent effective for treating nasal congestion and is commonly administered orally and concomitantly with an antihistamine for treatment of nasal congestion

associated with allergic rhinitis. For example, 5 mg of loratadine and 120 mg of pseudoephedrine sulfate ("PES") in a matrix core repetab tablet product is available wherein the PES is equally distributed between the repetab tablet coating and barrier-coated core and wherein all the loratadine is in the coating. When the repetab tablet is placed in a stirred 0.1N HCl solution such as found in the stomach, all of the PES, as well as all of the loratadine, present in the repetab tablet coating dissolve within a one hour period in the stirred acidic medium. None of the PES in the core dissolves in the acidic medium in that the barrier coating on the core is acid-resistant. A basic medium (a simulated inestinal fluid) is required to dissolve the core-coating and release the remaining 50% of PES over a five-hour period. The repetab product is recommended for twice-a-day dosing for effectiveness. U. S. Patent 4,990,535 and 5,100,675 disclose a twice-a-day sustained release coated tablet wherein the tablet coating comprises loratadine, a hydrophilic polymer and polyethylene glycol, and the tablet core comprises acetaminophen, pseudoephedrine or a salt thereof, a swellable hydrophilic polymer and pharmaceutically acceptable excipients. Neither the twice-a-day sustained release tablet nor the twice-a-day repetab tablet makes obvious or discloses the once-a-day oral dosage composition of this invention.

The successful development of a formulation of a loratadine-pseudoephedrine once-a-day product would be desirable, but would require achieving a release rate profile for the pseudoephedrine component over an extended period in excess of twelve hours and preferably at least 16 hours while maintaining the safety and effectiveness of loratadine. Products containing non-sedating antihistamines in combination with

pseudoephedrine such as Seldane-D, a press-coated product of terfenadine and pseudoephedrine and Hismanal-D, a combination of pseudoephedrine prills and a separate astemizole tablet are known, but do not make obvious the extended release composition of this invention. Furthermore, the administration of terfenadine and astemizole products to humans has been found to cause adverse effects including cardiac arrhythmias and occurrence of these arrhythmias have increased when the terfenadine or astemizole products are co-administered with other drugs such as ketoconazole and erythromycin or upon overdose of the non-sedating anti-histamine.

It would be desirable for increased patient compliance to have an extended release oral dosage loratadine-pseudoephedrine composition effective and safe when used on a once-a-day basis for the treatment, management and/or mitigation of the signs and symptoms associated with the common cold, upper respiratory diseases, allergic rhinitis and nasal congestion.

SUMMARY OF THE INVENTION

We have discovered that a film-coating of loratadine on a core tablet containing a pseudoephedrine salt, preferably pseudoephedrine sulfate, in a specific polymer matrix provides immediate release of loratadine and extended release of pseudoephedrine sulfate from the matrix core over a period in excess of twelve hours.

Thus the present invention provides a film-coated extended release oral dosage composition comprising:

a. a matrix core comprising:

	mg/core
Pseudoephedrine Sulfate	120-360
Hydroxypropyl Methylcellulose 2208 100,000 cps	160-480
Ethylcellulose	40-120
Dibasic Calcium Phosphate Dihydrate	56-164
Povidone	20-60
Silicon Dioxide	6-12
and	
Magnesium Stearate	2-6
Matrix Core Weight Range:	400-1200mg

and

b. a coating on said core comprising:

	mg/tablet
Loratadine	5-15
Hydroxypropyl Methylcellulose 2910 6 cps	17-50
Polyethylene Glycol 400	0.25-5.0
Polyethylene Glycol 3350	3.4-10.2
Approximate Coating Weight Range:	26-80mg
Approximate Composition (Matrix core and coating) Weight Range:	426-1280mg

In a preferred aspects, the present invention provides film-coated extended release oral dosage composition comprising a

a. a matrix core comprising:

	mg/core
Pseudoephedrine Sulfate	240
Hydroxypropyl Methylcellulose 2208 100,000 cps.	160-480
Ethylcellulose	40-120
Dibasic Calcium Phosphate Dihydrate	56-164
Povidone	20-60

	mg/core
Silicon Dioxide	6-12
and	
Magnesium Stearate	2-6
Approximate Matrix Core Weight Range:	524-1082mg

and

b. a coating on said core comprising:

	mg/tablet
Loratadine	10
Hydroxypropyl Methylcellulose 2910 6 cps.	17-50
Polyethylene Glycol 400	0.25-5.0
Polyethylene Glycol 3350	3.4-10.15
Approximate Coating Weight Range:	31-75mg
Approximate Composition(Matrix Core and Coating) Weight Range:	555-1157mg

In a more preferred aspect, the present invention provides a film-coated extended release oral dosage composition comprising:

a. a matrix core comprising:

	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
and	
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800mg

and

b. a coating upon said core comprising:

	mg/tablet
Loratadine, Micronized	10
Hydroxypropyl Methylcellulose 2910 USP 6 cps	33
Polyethylene Glycol 400 NF	0.67
Polyethylene Glycol 3350 NF	6.75
Color Dispersion (Solids)	6.25
Approximate Coating Weight:	57mg
Approximate Composition (Matrix Core and Coating) Weight:	857mg

DETAILED DESCRIPTION OF THE INVENTION

We have discovered a unique oral dosage composition containing a specific selection of ingredients including specific amounts of a pseudoephedrine salt, preferably pseudoephedrine sulfate in a polymer matrix core and of loratadine in an immediate release polymer film coating on the core. The oral dosage composition of this invention provides (1) immediate release (i.e., within one hour after oral administration to a patient) of the total dose of loratadine to maintain the once-a-day efficacy of loratadine (2) the extended release of pseudoephedrine sulfate from the matrix polymer cover over a period of at least 12 preferably 12 to 16 hours and more preferably at least 16 hours from oral administration (3) reasonable dose size for enhancing patients' compliance and (4) a shelf life of at least 24 months.

In the course of development of the oral dosage composition of this invention, it was discovered that the selection of the specific polymers and of the specific ratios of such polymers for the polymer matrix core was critical

to achieve the desired extended release period of at least 12 hours, preferably 12 to 16 hours and more preferably for at least 16 hours for pseudoephedrine sulfate. For example, the use of hydroxypropyl methyl cellulose 4,000 cps or 15,000 cps as polymers in the matrix core did not provide this more preferred extended release period of at least 16 hours for dose of pseudoephedrine sulfate. We discovered that only by selecting for inclusion into the matrix core specific weight ratios of three specific polymers was the desired pseudoephedrine release profile achieved. Only by combining (1) four parts by weight of hydroxypropyl methyl cellulose 2208 USP, 100,000 cps with (2) one part by weight of ethyl cellulose together with (3) one-half part by weight of povidone as a secondary binder was the more preferred extended release profile of at least 16 hours for pseudoephedrine sulfate from the matrix core achieved. The matrix core also contains specific amounts of silicon dioxide as a glidant and magnesium stearate as a lubricant. The tablet hardness 22 ± 6 Strong-Cobb Units (SCU) is not greatly affected by the higher level of lubricant (6mg/tablet) but it is preferred to maintain the lubricant level at 1/10 part by weight of lubricant to one part by weight of povidone as secondary binder.

The hydroxyl propyl methyl cellulose 2910 acts as a film-forming agent in the film coating, and the polyethylene glycols act as plasticizers. Other suitable film-forming polymers which may be used include hydroxypropyl cellulose, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose.

The oral dosage composition of this invention also provides a shelf life of more than 24 months, e.g., up to 36 and 48 months so long as the tablets are stored in standard package at between 2° and 30° C in an ambient environment.

In the preparation of the tablet core the povidone is dissolved in a mixture of alcohol and water. The pseudoephedrine sulfate, hydroxypropyl methylcellulose 2208 USP, 100,000 cps, ethylcellulose, and dibasic calcium phosphate are blended and granulated with the alcoholic water solution containing povidone. The granulation is milled, and dried to a loss on drying between 0.5 to 2.0%.

The dried granulation is milled and blended with requisite amounts of silicon dioxide and magnesium stearate. The final blend is compressed to produce the oral dosage composition in the preferred form of a tablet.

The coating is normally applied to the tablet cores in the following manner:

Cores are charged into a suitable coating pan. A water dispersion of hydroxypropyl methylcellulose 2910 USP and polyethylene glycol 3350 NF is applied to the cores. These sub-coated cores are then coated with a dispersion of loratadine, hydroxypropyl methylcellulose 2910 USP, polyethylene glycol 3350 NF and white color dispersion. This is followed by an application of polishing coating dispersion containing hydroxypropyl

methylcellulose and polyethylene glycol 400 NF. The coated tablets are then branded (with black ink) and packaged in plastic bottles and blisters for storage at a temperature between 2° and 30°C in an ambient environment

EXAMPLE I

This example illustrate preparation of the preferred oral dosage composition of this invention. The ingredients and specific amounts thereof are listed below.

I. Tablet Core

A. Method of Manufacture

1. Dissolve povidone in a mixture of alcohol and water.

2. Combine the pseudoephedrine sulfate, hydroxypropyl methylcellulose 2208, ethylcellulose and dibasic calcium phosphate, dihydrate in a suitable mixing bowl and blend.

3. Granulate the blend from Step 2 with the solution from Step. I. pass the wet granulation through a screen.

4. Dry the granulation to a loss on drying between 0.5 to 2.0% as determined by a moisture balance or equivalent.

5. Pass the dried granules through a screen.

6. Add the requisite amount of silicon dioxide and magnesium stearate to the dried, milled granules and blend.

7. Compress the blend on a suitable tablet press.

During the compression operation, representative samples of the cores are taken and in-process tests are performed.

The core matrix meets the following specification:

Weight: 800 ± 5% (mg)

Thickness: 0.280 ± 0.010 inches

Hardness: 22 ± 6 Strong-Cobb Units

The cores are coated in the following manners:

A. Preparation of Coating Dispersions and Solutions

I. Sub-Coating Solution

(l) Disperse hydroxypropyl methylcellulose USP 2910 and polyethylene glycol 3350 in a portion of hot purified water.

(2) Add the remainder of the purified water and cool the solution to room temperature.

2. Active Coating Dispersion

(I) Disperse hydroxypropyl methylcellulose USP 2910 and polyethylene glycol 3350 in a portion of hot purified water. Add additional water and cool the dispersion to room temperature.

(2) Disperse Loratadine in the remaining portion of room temperature purified water. Combine with hydroxypropyl methylcellulose/polyethylene glycol dispersion (Step I).

(3) Add white color dispersion. Mix until uniform.

3. Polishing Coating Solution

(I) Disperse hydroxypropyl methylcellulose USP 2910 and polyethylene glycol 400 in a portion of hot purified water.

(2) Add the remainder of the purified water and cool the solution to room temperature.

B. Coating of Tablet Core

(I) Charge the requisite quantity of tablet cores to a suitable coating pan.

(2) Apply the sub-coating solution.

(3) Quantitatively apply the active coating dispersion

(4) Apply the polishing coating solution

C. Branding

(I) Brand the coated tablets with black imprinting ink.

The preferred composition of the tablet core and coating is given below

Tablet Matrix Core

	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP I00,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	I08
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800mg

Tablet Coating

	mg/tablet
Loratadine, Micronized	I0
Hydroxypropyl Methylcellulose 29I0 USP 6 cps	33
Polyethylene Glycol 400 NF	0.67
Polyethylene Glycol 3350 NF	6.75
Color Dispersion (Solids)	6.25
Imprinting Ink	
Approximate Coating Weight:	57mg
Approximate Tablet (Matrix Core and Coating) Weight:	857mg

The in vitro dissolution profile of the tablet of Example I was measured in a stirred 0.IN HCl solution at 37°C (1st hour) and thereafter (for

an additional 15 hours) in a stirred phosphate buffer having a pH of 7.5 at 37°C. The loratadine in the coating was dissolved within the first hour and the total dose of pseudoephedrine sulfate in the core was slowly released via erosion and dissolution mechanisms over a period of at least 16 hours (see Table A hereinafter).

Similar results would be expected if a decongestant effective amount of another pharmaceutically acceptable pseudoephedrine salt, e.g., pseudoephedrine chloride were used in place of pseudoephedrine sulfate.

TABLE A

IN VITRO DISSOLUTION PROFILE OF LORATADINE AND PSEUDOEPHEDRINE SULFATE ("PES") FROM EXTENDED RELEASE TABLETS OF EXAMPLE I

	% Dissolved	
Time, Hour	Loratadine[a]	PES[b]
1	97	25
2	--	37
4	--	53
6	--	64
8	--	74
10	--	82
12	--	88
16	--	96

a Medium: 1000 ml 0.IN HCL, 37°C; USP Paddle, l00 rpm; average of l2 tablets.

b Medium: 1000 ml purified water, 37°C; USP Paddle, l00 rpm; average of l2 tablets.

What is Claimed is: -

1. A film-coated extended release oral dosage composition comprising:

a. a matrix core comprising:

	mg/core
Pseudoephedrine Sulfate	120-360
Hydroxypropyl Methylcellulose 2208 100,000 cps	160-480
Ethylcellulose	40-120
Dibasic Calcium Phosphate Dihydrate	56-164
Povidone	20-60
Silicon Dioxide	6-12
and	
Magnesium Stearate	2-6
Matrix Core Weight Range:	400-1200mg

and

b. a coating on said core comprising:

	mg/tablet
Loratadine	5-15
Hydroxypropyl Methylcellulose 2910 6 cps	17-50
Polyethylene Glycol 400	0.25-5.0
Polyethylene Glycol 3350	3.4-10.2
Approximate Coating Weight Range:	26-80mg
Approximate Composition (Matrix Core and Coating) Weight Range:	426-1280mg

2. A method of treating patients showing the signs and symptoms associated with upper respiratory diseases and nasal congestion which comprises administering to such a patient the oral dosage composition of Claim 1.

3. The oral dosage composition of Claim 1 wherein 240 mg. of pseudoephedrine sulfate is in the matrix core and 10 mg. of loratadine is in the coating.

4. A film-coated extended release oral dosage composition comprising:

a. a matrix core comprising:

	mg/core
Pseudoephedrine Sulfate	240
Hydroxypropyl Methylcellulose 2208 100,000 cps.	160-480
Ethylcellulose	40-120
Dibasic Calcium Phosphate Dihydrate	56-164
Povidone	20-60
Silicon Dioxide and Magnesium Stearate	6-12 / 2-6
Approximate Matrix Core Weight Range:	524-1082mg

and

b. a coating on said core comprising:

	mg/tablet
Loratadine	10
Hydroxypropyl Methylcellulose 2910 6 cps.	17-50
Polyethylene Glycol 400	0.25-5.0
Polyethylene Glycol 3350	3.4-10.2
Approximate Coating Weight Range:	31-75mg

Approximate Composition (Matrix Core and Coating) Weight Range: 555-1157mg

5. A method of treating a patient showing the signs and/or symptoms associated with upper respiratory diseases and nasal congestion which comprises administering to such a patient the oral dosage form of Claim 4.

6. A film-coated extended release oral dosage composition comprising:

a. a matrix core comprising:

	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF and Magnesium Stearate NF	8 and 4
Approximate Matrix Core Weight:	800mg

and

b. a coating upon said core comprising:

	mg/tablet
Loratadine, Micronized	10
Hydroxypropyl Methylcellulose 2910 USP 6 cps	33
Polyethylene Glycol 400 NF	0.67
Polyethylene Glycol 3350 NF	6.75
Color Dispersion (Solids)	6.25
Approximate Coating Weight	57mg
Approximate Composition (Matrix Core and Coating) Weight:	857mg

7. A method of treating a patient suffering from the signs and symptoms associated with upper respiratory disease and nasal congestion which comprises administering to such a patient the oral dosage composition of claim 6.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 93/09873

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 396 404 (SCHERING CORPORATION) 7 November 1990 see the whole document & US,A,4 990 535 (SCHERING) cited in the application	1-7
Y	US,A,4 601 894 (HANNA ET AL.) 22 July 1986 see the whole document see column 4; example 2	1-7
Y	EP,A,0 309 157 (AMERICAN HOME PRODUCTS) 29 March 1989 see the whole document	1-7
A	EP,A,0 311 067 (MERRELL DOW PHARMACEUTICALS INC.) 12 April 1989	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 1994	25. 01. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	BENZ, K

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter ional application No.
PCT/US93/09873

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 2,5,7 are directed to a method of treatment of the treatment of the human/animal body the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/US 93/09873

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0396404	07-11-90	US-A-	4990535	05-02-91
		AU-B-	628986	24-09-92
		AU-A-	5664890	29-11-90
		CA-A-	2054752	04-11-90
		EP-A-	0471009	19-02-92
		JP-T-	4501425	12-03-92
		WO-A-	9013295	15-11-90
		US-A-	5100675	31-03-92
US-A-4990535	05-02-91	AU-B-	628986	24-09-92
		AU-A-	5664890	29-11-90
		CA-A-	2054752	04-11-90
		EP-A-	0396404	07-11-90
		EP-A-	0471009	19-02-92
		JP-T-	4501425	12-03-92
		WO-A-	9013295	15-11-90
		US-A-	5100675	31-03-92
US-A-4601894	22-07-86	CA-A-	1272957	21-08-90
		US-A-	4695591	22-09-87
		US-A-	4657757	14-04-87
EP-A-0309157	29-03-89	AU-A-	2215388	11-05-89
		CA-A-	1318600	01-06-93
		GB-A,B	2209940	01-06-89
		JP-A-	2270820	05-11-90
		US-A-	4966768	30-10-90
EP-A-0311067	12-04-89	AU-A-	2345988	20-04-89
		CA-A-	1314485	16-03-93
		DE-A-	3874072	01-10-92
		JP-A-	1128925	22-05-89
		US-A-	4996061	26-02-91